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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,082	06/14/2001	David James Craik	DAVI-0005	1485

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 12/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,082	CRAIK ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 17-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-15 and 17-19* is/are rejected.

7)☒ Claim(s) *10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9/11/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. Claims 1-15 and 17-19 are pending.

Applicants' amendment filed on July 10, 2003 is acknowledged. Applicants' response has been fully considered. Claims 1, 3, 7, 13-15 and 17 have been amended, claim 16 has been cancelled, and claim 19 has been added. Thus, claims 1-15 and 17-19 are examined.

Rejection Withdrawn

Claim Rejections - 35 USC § 101

2. The previous objection of claim 1 under 35 U.S.C. 101, is withdrawn in view of applicant's amendment to the claim, and applicant's response at page 6 in the amendment filed July 10, 2003.

3. The previous objection of claims14 and 16 under 35 U.S.C. 101, regarding the claimed recitation of a use, without setting forth any steps involved in the process, is withdrawn in view of applicant's amendment to the claim, applicant's cancellation of the claim, and applicant's response at page 6 in the amendment filed July 10, 2003.

Claim Rejections - 35 USC § 112

4. The previous rejection of claim 16 under 35 U.S.C.112, first paragraph, is withdrawn in view of applicant's cancellation of the claim in the amendment filed July 10, 2003.

5. The previous rejection of claims 3, 7, 13 and 16 under 35 U.S.C.112, second paragraph, is withdrawn in view of applicant's amendment to the claim, applicant's cancellation of the claim, and applicant's response at page 10 in the amendment filed July 10, 2003.

Claim Rejections - 35 USC § 102

6. The previous rejection of claims 1-4, 15 and 16 under 35 U.S.C. 102(b) as being anticipated by Olivera *et al.* (U. S. Patent 4,447,356), is withdrawn in view of applicant's amendment to the claim, applicant's cancellation of the claim, and applicant's response at pages 11-12 in the amendment filed July 10, 2003.

7. The previous rejection of claims 1, 3 and 5 under 35 U.S.C. 102(b) as being anticipated by Pallaghy *et al.* (Protein Science 3, 1833-1839 (1994)), is withdrawn in view of applicant's amendment to the claim, and applicant's response at pages 11-12 in the amendment filed July 10, 2003.

8. The previous rejection of claims 1-4, 15 and 16 under 35 U.S.C. 102(b) as being anticipated by Shon *et al.* (WO 96/33206), is withdrawn in view of applicant's amendment to the claim, applicant's cancellation of the claim, and applicant's response at pages 11-12 in the amendment filed July 10, 2003.

Claim Objections

9. Claim 1 is objected to because of the use of "no free N- or C-termini". Since there is only one N- or C-terminus in the conotoxin peptide, use of "no free N- or C-terminus" is suggested.

10. Claim 2 is objected to because of the use of "A cyclised conotoxin peptide according to claim 1". Since claim 2 is dependent from claim 1, use of "The cyclised conotoxin peptide according to claim 1" is suggested. See also claims 2-15, 17 and 18.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-9, 11-15 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cyclised conotoxin peptide such as SEQ ID NOs:5-9 having disulfide bonds and an amide cyclized backbone linked at N- and C-termini, where the amino acid sequence is defined; a process of preparing the cyclic conotoxin; and a composition comprising the cyclic conotoxin, does not reasonably provide enablement for a cyclized conotoxin peptide having an amide cyclized backbone with no free N- or C-terminus, where the amino acid sequence is not defined; a process of preparing the cyclic conotoxin; a composition comprising the cyclic conotoxin; a method of detecting a neurological disorder or an undefined method comprising administering the cyclic conotoxin, where the neurological disorder or the method is not defined. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-9, 11-15 and 17-19 are directed to a cyclic conotoxin peptide having an amide cyclized backbone with no free N- or C-terminus (claims 1-9); a process of preparing the cyclic conotoxin (claims 11-13 and 19); a composition comprising the cyclic conotoxin (claims 17 and 18); a method of detecting a neurological disorder (claim 14); or a method comprising administering the cyclic conotoxin (claim 15). The specification, however, only discloses cursory conclusions without data supporting the findings, which states that cyclization of the peptide backbone of conotoxin to produce non-natural analogs results in new molecules which can retain the therapeutic activity of the non-cyclized peptide (page 2, lines 9-11). There are no

indicia that the present application enables the full scope in view of the cyclized conotoxin peptide having an amide cyclized backbone with no free N- or C-terminus and the method of detecting a neurological disorder using the cyclized conotoxin as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the cyclized conotoxin peptides, and the conditions of detecting various neurological disorders using cyclized conotoxin peptides, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

The specification indicates the preparation and activities of cyclic MVIIA conotoxins (Examples 1-3, 5) and MII α-conotoxins (Example 6). However, there are no other working examples demonstrating activities of various cyclized conotoxin peptides.

(3). The state of the prior art and relative skill of those in the art:

The related art (e.g., Shon *et al.*, WO 96/33206) indicates μ-conotoxin PIIIA, which is a sodium channel blocker, is useful as active agent for treating urinary or fecal incontinence.

However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on identities of various cyclized conotoxin peptides other than cyclo-MVIIA conotoxins and cyclo-MII α-conotoxins, the conditions for detecting various biological diseases, and the effects of various cyclized conotoxin peptides in the treatment to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a cyclized conotoxin peptide having an amide cyclized backbone with no free N- or C-terminus, and a method of detecting a neurological disorder comprising administering the cyclic conotoxin. However, the specification does not show various cyclized conotoxin peptides other than cyclo-MVIIA conotoxins and cyclo-MII α-conotoxins, nor demonstrates the effects of the peptides in detecting neurological disorders, the invention is highly unpredictable regarding the activity of the cyclic conotoxin and the outcome of the treatment using an unidentified cyclized conotoxin peptide which does not have a defined sequence. For example, Armishaw *et al.* (American Peptide Society, pages113-114, 2001) teaches the synthesis of two N to C terminal cyclic analogs of α-conotoxin ImI (GCCSDPRCAWRC-NH_2), cImI-AG (having Ala-Gly spacer) and cImI-A (having Ala spacer), which indicates the major product of cImI-AG has 1-3, 2-4 S-S connectivity and the major isomer of cImI-A has 1-4, 2-3 S-S connectivity, while the linear α-conotoxin ImI has 1-3, 2-4 S-S connectivity (see whole documant). The reference also indicates the cyclization of α-conotoxin ImI results in 30-fold decrease in receptor binding activity. Thus, despite having the three dimensional structure of ImI, which shows the close proximity of the termini and the position of the active site residues, and having experience in cyclizing peptide, the reference

illustrate how unpredictable regarding the cyclization of conotoxin peptide and its receptor binding activity.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a cyclized conotoxin peptide having an amide cyclized backbone with no free N- or C-terminus, a process of preparing the cyclic conotoxin, a composition comprising the cyclic conotoxin, a method of detecting neurological disorders, and an unidentified method comprising administering the cyclized conotoxin peptide. The specification indicates the preparation of cyclic MVIIA conotoxins (Examples 1, 2) and cyclic MII α-conotoxins (Example 6), and the cyclic MVIIA conotoxins act as the antagonists specific for N-type voltage-sensitive calcium channels (Example 3). The specification also indicates omega-conotoxins which block N-type calcium channels may be useful for the treatment of neurological disorders (page 15, line 23-page 16, line 1). However, the specification has not shown the identities of various cyclized conotoxin peptides other than cyclic MVIIA conotoxins and cyclic MII α-conotoxins. Furthermore, the specification has not demonstrated the use of any cyclized peptide in detecting specific neurological disorders or in the treatment of specific diseases. There are no working examples indicating the effects of the cyclized conotoxin peptides in detecting various neurological disorders. Since the specification has not provided sufficient teachings on identities of various cyclized conotoxin peptides and the conditions for detecting various neurological disorders, thus, it is necessary to have additional guidance on amino acid sequences of various cyclized conotoxin peptides, and the detection of various neurological disorders using the cyclized conotoxin peptides, and to carry out further

experimentation to assess the effects of various cyclized conotoxin peptides in detecting various neurological disorders and the treatment of specific diseases.

(6). Nature of the Invention

The scope of the claims encompass various cyclized conotoxin peptides and a method of detecting various neurological disorders comprising administering the cyclic conotoxin, but the specification only shows the making of cyclic MVIIA conotoxins and cyclic MII α-conotoxins, and the cyclic MVIIA conotoxins acting as the antagonists specific for N-type voltage-sensitive calcium channels, it has not demonstrated the use of any cyclized conotoxin peptide in the detecting various neurological disorders. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, the outcome of treatment is unpredictable using the claimed variants, and the teachings are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effect of the cyclized conotoxin in detecting various neurological disorders.

In response, applicants indicate conotoxin peptides have been known for many years and there is vast amount of literature describing such peptides, methods for their preparation, as well as their use in therapy, e.g., both Olivera *et al.* (U. S. Patent 4,447,356) and Shon *et al.* (WO 96/33206) provide guidance on how to synthesize conotoxin peptides and assess the activity o the newly synthesized conotoxin peptides, and the specification indicates the references of synthesizing linear conotoxin peptides and the method of cyclizing linear conotoxins (Examples 1, 2, 5 and 6), thus, a skilled practitioner would be able to routinely cyclize known conotoxin

peptides according to the methods of the present invention. Applicants further assert despite the vast amount of literature on conotoxin peptides, however, there are no art describing or suggesting to connect the N- and C- termini to form an amide cyclized version of such peptides, the instant invention discovers that cyclization of known conotoxin peptides described in the art results in novel compounds retaining therapeutic activity of the original non-amide cyclized peptides; the Office Action's assertion of undue breadth appears based on the assumption that enablement requires an exemplification of all possible uses of the claimed invention, e.g., the showing of an effective treatment of a disease using the claimed conotoxin peptides, and the possibility that cyclized peptide has activity but is not able to entirely remedy a disease state does not render the claims non-enabled, it is improper for the PTO to require any showing the degree of effectiveness of therapeutic inventions, enablement requires only the application how to make and use the invention without undue experimentation (pages 7-10 of the response). The response has been fully considered, however, the argument is not found persuasive because the claims are directed to cyclized conotoxins having an amide cyclized backbone, which not only includes cyclization of known linear conotoxins, but also cyclization of unknown conotoxins with undefined structures. Since the structure of the linear conotoxin is not defined, a person skilled in the art would not be able to make and use the cyclized conotoxin. Furthermore, the claimed cyclized conotoxin, which contains an extra cyclic structure, is structurally different from the parent conotoxin peptide, thus the activity of this cyclized conotoxin needs to be tested for its use, e.g., Armishaw *et al.* (2001) indicates cyclization of α-conotoxin ImI results in different S-S connectivity in different analogs and in 30-fold decrease in receptor binding activity, thus, it is unpredictable regarding the cyclization of conotoxin peptide and the receptor binding activity of

the cyclized conotoxin peptide (see the section of Predictability or unpredictability of the art). Regarding the requirement of showing effective treatment of a disease using the claimed conotoxin peptide, since the claimed method is directed to a method of detecting a neurological disorder using the cyclized conotoxin, it is necessary to show the effect of the cyclized conotoxin in the treatment. However, as indicated in the section above, the specification does not provide sufficient teachings regarding the claimed method, thus it is necessary to carry out further experimentation to assess the effect of the cyclized conotoxin in detecting various neurological disorders.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 14 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claims 14 is indefinite because the claim lacks essential steps as claimed in the process of detecting a neurological disorder. The omitted steps are the step of detecting the neurological disorder and the outcome of the treatment. Claim 15 is also indefinite as to "a neurological disorder", it is not clear which neurological disorder is referred to.

14. Claims 15 is indefinite because the claim only recites "a method" without indicating what the method for, it is not clear what the method is, and what the cyclic conotoxin at effective amount would do?

15. Claim 10 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

16. Claims 1-9 and 11-19 are rejected and claim 10 is objected to.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers

for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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December 16, 2003

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
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